

Amendments to the Specification

Please replace the paragraph beginning at page 11, line 24, with the following paragraph:

--In a preferred embodiment of the present invention, the targeting construct is prepared directly from a plasmid genomic library using the methods described in U.S. Patent No. 6,815,185 issued November 9, 2004, which is based on U.S. Patent Application No. 09/885,816, filed June 19, 2001, which is a continuation of U.S. Patent Application No. 09/193,834, filed November 17, 1998, now abandoned, which claims priority to U.S. Provisional Application No. 60/084,949, filed May 11, 1998, and U.S. Provisional Application No. 60/084,194, and pending U.S. Patent Application Ser. No.: 08/971,310, filed November 17, 1997, which was converted to U.S. Provisional Application No. 60/084, 949, filed May 11, 1998, the disclosure of Provisional Application No. 60/084,194 which is incorporated herein in its entirety. Generally, a sequence of interest is identified and isolated from a plasmid library in a single step using, for example, long-range PCR. Following isolation of this sequence, a second polynucleotide that will disrupt the target sequence can be readily inserted between two regions encoding the sequence of interest. In accordance with this aspect, the construct is generated in two steps by (1) amplifying (for example, using long-range PCR) sequences homologous to the target sequence, and (2) inserting another polynucleotide (for example a selectable marker) into the PCR product so that it is flanked by the homologous sequences. Typically, the vector is a plasmid from a plasmid genomic library. The completed construct is also typically a circular plasmid.

Please replace the paragraph beginning at page 12, line 6, with the following paragraph:

In another embodiment, the targeting construct is designed in accordance with the regulated positive selection method described in U.S. Patent Application Ser. No. 09/954,483, filed September 17, 2001-2000, now U.S. Patent Publication

No. 20030032175. the disclosure of which is incorporated herein in its entirety.

The targeting construct is designed to include a PGK-*neo* fusion gene having two *lacO* sites, positioned in the PGK promoter and an NLS-*lacI* gene comprising a lac repressor fused to sequences encoding the NLS from the SV40 T antigen.--